REMARKS

Claims 1-2 and 4-47 are currently pending in the present application. Claims 1, 2, 11, 12, 15-18 and 20 have been amended in the expectation that the amendments will place this application in condition for allowance. The amendments do not introduce new matter within the meaning of 35 U.S.C. § 132. Accordingly, entry of the amendments is respectfully requested.

1. Rejection of Claims 1-7, 9-15, 21-22, 25-29, 33-34, 37-41 and 45 under 35 USC §102(e)

The Official Action states that claims 1-7, 9-15, 21-22, 25-29, 33-34, 37-41 and 45 are rejected under 35 U.S.C. § 102(e) as being anticipated by Akiyama et al. (US Patent No. 5,948,773)

As the basis of this rejection, the Official Action states:

> Akiyama discloses a pharmaceutical formulation comprising an antibacterial substance and/or an anti-ulcer substance, in that the anti-ulcer substance is a proton pump inhibitor, wherein at lease either one of them is formulated into a gastrointestinal mucosa-adherent solid preparation, which comprises a matrix containing a combination mixture of fatty acid esters, lipids and viscogenic agents, whereby lipids include saturated fatty acids or salts thereof, higher alcohols—cetyl alcohol, stearyl alcohol, fatty acid glycerol esters (mono-, di- or triglycerides), waxes, hydrocarbons—paraffin, microcrystalline wax and phospholipids) in combination with pharmaceutically acceptable excipients (see reference column 2, line 16 through col. 3, line 67); (col. 9, line 20, through col. 13, line 59).

Applicants respectfully traverse this rejection. The test for anticipation is whether each and every element as set forth is

found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987); MPEP § 2131. The identical invention must be shown in as complete detail as is contained in the claim. *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989); MPEP § 2131. The elements must also be arranged as required by the claim. *In re Bond*, 15 USPQ2d 1566 (Fed. Cir. 1990).

Applicants have amended claims 1, 2, 11, 12, 15-18 and 20 to obviate the present rejection under 35 USC §102(e). The presently claimed invention now relates to administration forms for acid-labile active compounds, comprising pharmaceutical excipients and multiple individual active compound units, wherein the individual active compound units are microspheres. Basis for the amendment can be found throughout the specification and in particular, on pages 10 and 13-16.

In contrast, Akiyama relates to a gastrointestinal mucosa-adherent solid preparation, which adheres to a particular site in the gastrointestinal tract. In particular, Akiyama discloses that the preparation contains polyglycerin fatty acid esters and preferably such polyglycerin fatty acid esters or lipids in combination with a viscogenic agent. The viscogenic agent is said to become viscous and adherent to the gastrointestinal tract mucosa upon exposure to water. The lipids disclosed by Akiyama comprise a

myriad of different types of lipids and no specific combination is disclosed. Akiyama does not disclose a formulation wherein an acid-labile active compound is present in microspheres in a matrix made of a mixture comprising at least one fatty alcohol and at least one solid paraffin.

Thus, Akiyama et al. fail to teach each and every element of the presently claimed invention as required by *Verdegaal Bros. v. Union Oil Co. of California* and therefore fails the test for anticipation under 35 U.S.C. §102(e).

Accordingly, applicants respectfully request the Examiner to reconsider and withdraw the rejection of claims 1-7, 9-15, 21-22, 25-29, 33-34, 37-41 and 45.

2. Rejection of Claims 8, 16-20, 23, 24, 30-32, 35, 36, 42-45 and 47 under 35 USC §103(a)

The Official Action states that claims 8, 16-20, 23, 24, 30-32, 35, 36, 42-45 and 47 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Akiyama et al. in view of Linder et al.

In particular, the Official Action states the following:

> Akiyama, as discussed above, teaches a pharmaceutical formulation comprising an antibacterial substance and/or an anti-ulcer substance, in that the anti-ulcer substance is a proton pump inhibitor, wherein at least either one of them is formulated into a gastrointestinal mucosa-adherent solid preparation, which comprises a matrix containing a combination mixture of fatty acid esters, lipids and viscogenic agents, whereby lipids include saturated fatty acids or salts thereof, higher alcohols–

cetyl alcohol, stearyl alcohol, fatty acid glycerol esters (mono-, di- or triglycerides), waxes, hydrocarbons- paraffin, microcrystalline wax and phospholipids) in combination with pharmaceutically acceptable excipients (see reference column 2, line 16 through col. 3, line 67); (col. 9, line 20 through col. 13, line 59).

The anti-ulcer substance includes H2 blockers and proton pump inhibitors, wherein proton pump inhibitors are preferred. The proton pump inhibitors include benzimidazole compounds such as lansoprazole, timoprazole, omeprazole and pantoprazole, for example (col. 3, lines 55-67; col. 9, lines 20-34). The salt of a benzimidazole compound is preferably used as a physiologically acceptable salt. Physiologically acceptable salts include salts with *inorganic bases*, salts with organic bases and salts with basic amino acids (col. 9, lines 39-49).

The formulation of the invention is used as (1) a combination of an anti-ulcer substance and a gastrointestinal mucosa-adherent solid preparation containing an antibacterial substance, (2) a combination of an antibacterial substance and a gastrointestinal mucosa-adherent solid preparation containing an anti-ulcer substance, (3) a gastrointestinal mucosa-adherent solid preparation containing both an antibacterial substance and an anti-ulcer substance, or (4) a combination of a gastrointestinal mucosa-adherent solid preparation containing an antibacterial substance and a gastrointestinal mucosa adherent solid preparation containing an anti-ulcer substance. The combination of an anti-ulcer substance and a gastrointestinal mucosa-adherent solid preparation containing an antibacterial substance is preferred (col. 9, lines 53-67).

Akiyama teaches that the matrix containing a polyglycerol fatty acid ester may also incorporate a lipid. The lipid is a water-soluble substance that serves to control the dissolution rate of active ingredients, exemplified by the previously mentioned lipids (col. 13, lines 12-16).

The solid preparation may incorporate additives that include excipients, such as lactose, corn starch, talc, crystalline cellulose; binders, such as sucrose, methyl cellulose, polyvinylpyrrolidone, etc.; disintegrating

agents, wetting agents, stabilizers and the like (col. 13, lines 28-52).

Example compositions for oral administration include tablets, pills, granules, powders, capsules, syrups, emulsions, and suspensions. These compositions are produced by known methods, using lactose, starch, sucrose, magnesium stearate and other substances as carriers or excipients (col. 17, lines 25-29).

Akiyama teaches the inclusion of lipids in the formulation, but is deficient only in the sense that he does not explicitly teach the selected sterols in the formulation.

Linder teaches an administration form comprising acid-labile proton pump inhibitors comprising the use of at least one sterol, whereby suitable sterols include phytosterols, such as ergosterol, stigmasterol, sitosterol, brassicasterol and campesterol and zoosterols, such as cholesterol and lanosterol or mixtures thereof. (See reference column 2, line 45 through column 4, line 15).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention was made to use the teachings of Linder within the teachings of Akiyama because Linder explicitly teaches that various sterols can be used in the proton pump inhibiting composition and Akiyama teaches also various lipids can be formulated in the anti-ulcer composition. The expected result would be an improved proton pump inhibiting composition for the effective treatment of a disease, as similarly desired by applicant.

The rejection is maintained and applied to newly added claims 21-47.

Akiyama discloses a proton pump inhibitor pharmaceutical formulation which comprises a matrix containing a combination mixture of fatty acid esters, lipids and viscogenic agents, whereby lipids include saturated fatty acids or salts thereof, higher alcohols--cetyl alcohol, stearyl alcohol, fatty acid glycerol esters (mono-, di- or triglycerides), waxes, hydrocarbons- paraffin, microcrystalline wax and phospholipids) in combination with pharmaceutically acceptable excipients (see

reference column 2, line 16 through col. 3, line 67); (col. 9, line 20 through col. 13, line 59). The proton pump inhibitors include benzimidazole compounds such as lansoprazole, timoprazole, omeprazole and pantoprazole, for example (col. 3, lines 55-67;col.9, lines 20-34). Oral administration forms include tablets, pills, granules, powders, capsules, syrups, emulsions and suspensions. The granules taught by Akiyama have a particle size of up to approximately 1400 microns.

Akiyama is deficient in the sense that he does not explicitly teach pure enantiomer and esomeprazole.

Linder ('993) obviates this deficiency by teaching acid-labile active proton pump inhibitors wherein the acid-labile proton pump inhibitors also include the pure enantiomers of the acid-labile proton pump inhibitors and their mixtures (see col. 3, lines 58-64). Additionally, Linder teaches at col. 9, claim no. 6, that the acid-labile proton pump inhibitor can be one of esomeprazole.

Regarding the use of the specified solid paraffin, Akiyama teaches the generic concept of adding hydrocarbons, such as paraffins, and thus would include various types of paraffin as those instantly claimed.

With respect to the specified triglyceride (i.e. tristearate, tripalmitate, trimyristate) and fatty acid ester (cetyl palmitate), Akiyama recognizes the incorporation of triglycerides, such as monopalmitin and fatty acid esters, such as polyglycerin fatty acid esters of any type. Furthermore, particular ingredients, such as those instantly claimed, could be determined by one of ordinary skill in the art, based on the purpose intended.

Applicants have not shown any unexpected or surprising results that accrue from the use of the instantly named ingredients.

Applicants respectfully traverse the rejection of claims 8, 16-20, 23, 24, 30-32, 35, 36, 42-45 and 47. The references of record do not teach or suggest applicants' inventive subject matter as a whole as recited in the claims. The Examiner has failed to

establish a *prima facie* case of obviousness against the presently rejected claim.

To establish a *prima facie* case of obviousness, the PTO must satisfy three requirements. First, the prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention, must contain some suggestion or incentive that would have motivated the skilled artisan to modify a reference. *In re Fine*, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen Inc. v. Chugai Pharm. Co.*, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991). Lastly, the prior art references must teach or suggest all the limitations of the claims. *In re Wilson*, 165 USPQ 494, 496 (C.C.P.A. 1970).

As stated above with reference to the rejection under 35 USC §102(e), the amendment to claims 1, 2, 11, 12, 15-18 and 20 obviates the present rejection under 35 USC §103(a). The presently claimed invention now relates to administration forms for acid-labile active compounds, comprising pharmaceutical excipients and multiple individual active compound units, <u>wherein the individual active compound units are microspheres</u>. Basis for the amendment can be found throughout the specification and in particular, on pages 10 and 13-16.

In contrast, Akiyama relates to a gastrointestinal mucosa-adherent solid preparation, which adheres to a particular site in the gastrointestinal tract. In particular, Akiyama discloses that the preparation contains polyglycerin fatty acid esters and preferably such polyglycerin fatty acid esters or lipids in combination with a viscogenic agent. The viscogenic agent is said to become viscous and adherent to the gastrointestinal tract mucosa upon exposure to water. The lipids disclosed by Akiyama comprise a myriad of different types of lipids and no specific combination is disclosed. Akiyama does not disclose a formulation wherein an acid-labile active compound is present in microspheres in a matrix made of a mixture comprising at least one fatty alcohol and at least one solid paraffin.

Further, Applicants are unsure why the Examiner has presently rejected claims 16-20 under 35 USC §103(a), as they were previously rejected under 35 USC §102(e) in the Official Action dated March 12, 2003 and no amendments were made to those claims in the Response filed June 11, 2003. In any event, claims 16-20 are drawn to a specific process for the production of an active compound unit in the form of a microsphere comprising an acid-labile active compound, where the acid-labile active compound is present in the microsphere in a matrix comprising at least one fatty alcohol, by producing drops of a solution or dispersion of the acid-labile active compound in at least one fatty alcohol by means of vibrating

nozzles and solidifying the drops formed in a suitable medium. In contrast, the methods of preparation according to Akiyama disclosed in column 16, lines 37-49 and the Examples do not disclose the steps of the presently pending claims.

Thus, Akiyama fails to teach all the limitations of the claimed invention as required by *In re Wilson*.

Linder does not remedy these deficiencies. While Linder teaches a novel administration form for acid-labile active compounds, it does not teach an administration form for acid-labile active compounds comprising pharmaceutical excipients and multiple microspheres in a matrix comprising at least one fatty alcohol and at least one solid paraffin.

Thus, the references of record fail to teach or suggest all the limitations of the claims of the present invention as required by *In re Wilson*.

Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 8, 16-20, 23, 24, 30-32, 35, 36, 42-45 and 47.

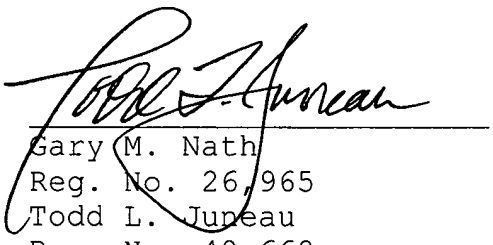
CONCLUSION

Based upon the above remarks, the presently claimed subject matter is believed to be novel and patentably distinguishable over the prior art of record. The Examiner is therefore respectfully requested to reconsider and withdraw the rejections of pending claims 1-2 and 4-47. Favorable action with an early allowance of the claims pending in this application is earnestly solicited.

The Examiner is welcomed to telephone the undersigned attorney if she has any questions or comments.

Respectfully submitted,

NATH & ASSOCIATES PLLC



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